REGULATION OF BLOOD FLOW

Learning objectives:

By the end of this lecture the student should be able to:

1. Explain local regulation of blood flow
2. Explain the significance of Autoregulation (myogenic and metabolic)
3. Compare short term and long-term regulation of blood flow
4. Compare active and reactive hyperemia
5. Compare the role of endothelium and platelets in local regulation of blood flow
6. Outline the effects of circulating hormones in blood flow regulation
7. Evaluate the role of vasoconstrictor hormones in regulation of blood flow
8. evaluate the role of vasodilator hormones in regulation of blood flow.
9. Explain the role of autonomic nervous system in controlling the blood flow
10. Apply knowledge to solve clinical problem

Control of the blood flow to the tissues is achieved by changing the diameter of the arterioles. The diameter of the arterioles in active tissues is regulated and adjusted by

A) Locally produced vasodilator metabolites.
B) Systemically circulating vasoactive substances
C) The sympathetic nervous system.

The systemic regulatory mechanism acts at the same time with the local mechanisms and adjust vascular responses throughout the body.

A-LOCAL REGULATION OF BLOOD FLOW

Local control of arteriolar diameter is carried out by:

I. Auto regulation It is the capacity of tissues to regulate their own blood flow.

- ◊ Myogenic
- ◊ Metabolic

II. Vasoactive substances secreted by the endothelium or the platelets

- Prostacyclin from endothelium
- Endothelial-Derived Relaxing Factor (EDRF):
- Endothelins
- Thromboxane A2 from platelets

I. Auto regulation:

◊ *a) Myogenic auto regulation:*

- ✓ It is the ability of vascular beds to compensate for moderate changes in perfusion pressure by changing the vascular resistance by an intrinsic capacity, so the blood flow remains relatively constant.
- ✓ Mechanism: This is achieved by the intrinsic contractile response of vascular smooth muscle to stretch. As the pressure rises, the blood vessels are distended and the vascular smooth muscle fibers contract.

Laplace law: It states that:

Vessel wall tension $\propto$ distending pressure $\times$ the radius of the vessel.
So, in order to maintain a given wall tension when pressure rises, a decrease in the vessel radius is required.

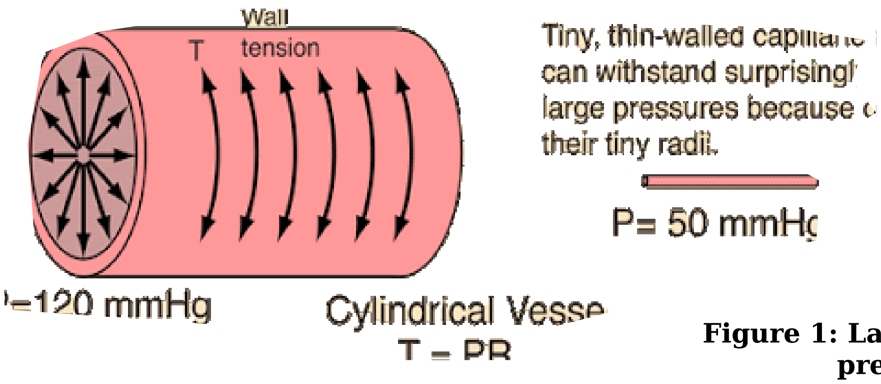

Figure 1: Laplace law: relationship between pressure and wall tension

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◊ *b) Metabolic autoregulation*

- ✓ The active tissue have metabolites (proportionate to the activity) that cause vasodilatation to increase the local blood flow.
- ✓ These metabolites cause relaxation of the arterioles and precapillary sphincters.
- ✓ The resulting increase in blood flow tends to wash these metabolites away.

Examples of metabolites that accumulate in tissues and cause vasodilator

1. Decrease in oxygen tension (Hypoxia in nearly all vascular beds, except in the pulmonary circulation).
2. Acidosis
3. Increases in CO_2 tension, its action is most pronounced in skin and brain.
4. Rise in temperature in active tissues.

5. K^+ and lactate in skeletal muscle.
6. Histamine in injured tissues.
7. Adenosine in cardiac muscle.

<u>Metabolic autoregulation can be either:</u>

1. ***Short- term*:** where the regulatory mechanisms last for minutes.
2. ***Long- term*:** where the regulatory mechanisms take place for days or years.

1. **Short- term metabolic autoregulation**

✓ *<u>Reactive hyperemia:</u>*

When the blood supply to a tissue is blocked for some time, and then the block is released , the resulting flow through this tissue usually increases about 5 times the normal. The duration of this hyperemia depends upon the duration of the block.

<u>Mechanism:</u>

The block of blood supply to the tissue causes the nutrients (including O_2) to be consumed and the vasodilator metabolites to accumulate. When the block is released, more blood will flow to the dilated metarterioles and precapillary sphincters. Figure 2

✓ *<u>Active hyperemia</u>*

When any tissue becomes highly active, such as a muscle during exercise, or a gastrointestinal gland during digestion, the rate of blood flow through the tissue increases. This phenomenon is called active hyperemia

<u>Mechanism:</u>

The increase in local metabolism causes the cells to consume the nutrients extremely rapidly, and also to release large quantities of vasodilator substances. This results in a dilatation of local blood vessels and an increase in local blood flow. In this way, the active tissue will receive the additional nutrients required to sustain its new level of function. Fig 2

Figure 2: reactive hyperemia

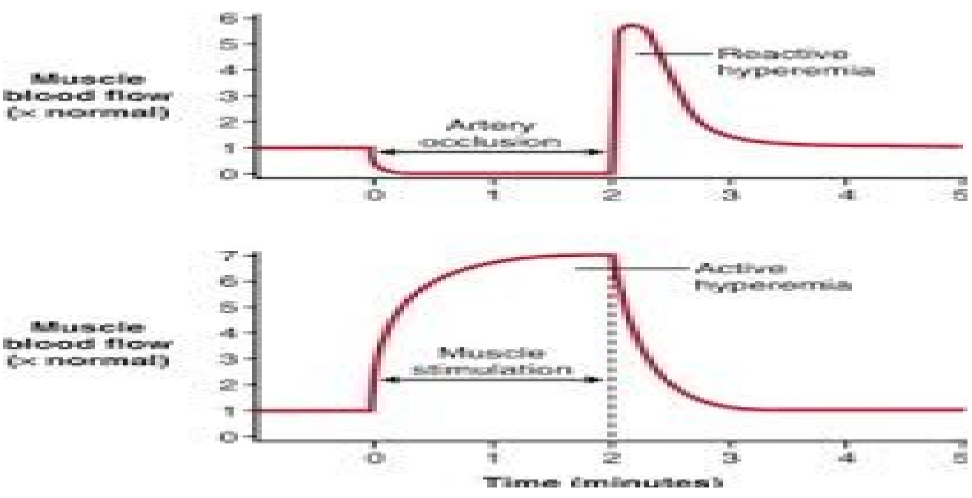

Figure 2: reactive hyperemia

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2. **Long -term metabolic autoregulation:**
   - ✓This happen when the tissue metabolism becomes abnormal (increased or decreased) or its local blood supply is changed.
   - ✓ the long term metabolic autoregulatory mechanisms automatically readjust the local blood flow over a period of weeks or months.
   - ✓The underlying mechanism of increased blood flow is that the resulting hypoxia will stimulate the production of certain factors causing **angiogenesis** (**increased tissue vascularity** and the **development of collaterals).**
   - ✓In young persons, this degree of readjustment is usually very exact; in old persons it is only partial.

II. Vasoactive substances secreted by the endothelium or the platelets

a. Prostacyclin:

- ✓ It is produced by endothelial cells.
- ✓ It **inhibits** platelet aggregation and promotes ***vasodilatation***.

b. Endothelial-Derived Relaxing Factor (EDRF, NO):

- ✓ **Nitric oxide (NO).** NO is synthesized from arginine in a reaction catalyzed by nitric oxide synthase (NO synthase, NOS).
- ✓ It is a powerful ***vasodilator*** substance.
- ✓ Many vasodilator substances act through releasing of NO (e.g. acetylcholine, bradykinin, vasoactive intestinal peptide (VIP) and substance P).
- ✓ Tonic release of NO is essential for maintaining normal arterial blood pressure.

c. Endothelins:

- ✓ Three Endothelins are identified (1, 2, and 3).
- ✓ Endothelin-1, produced by endothelial cells, is one of the most potent ***vasoconstrictor*** agents.
- ✓ It contracts vascular smooth muscles; veins are more sensitive than arteries.

- ✓ It appears to be primarily a local paracrine regulator of vascular tone.

d. Thromboxane A2:
- ✓ It is produced by the platelets.
- ✓ It **promotes** platelet aggregation and ***vasoconstriction.***

N.B. The balance between platelet thromboxane A2 and prostacyclin enhances localized platelet aggregation and consequent clot formation, while preventing excessive extension of the clot and maintaining blood flow around it.

B. SYSTEMIC REGULATION OF BLOOD FLOW:

Systemic control of the arterioles **(extrinsic control)** is carried out by hormonal (***Humoral***) and nervous mechanisms.

I. HORMONAL CONTROL

a) Vasoconstrictor hormones: include norepinephrine, epinephrine, angiotensin II. & Antidiuretic hormone (ADH)

1. Norepinephrine-Epinephrine
   - ✓ Stimulation of the sympathetic nervous system not only causes direct nervous excitation of blood vessels and the heart, but also causes release by the adrenal medulla of **norepinephrine** and **epinephrine** into the circulating blood.
   - ✓ These two hormones circulate to all parts of the body and cause essentially the same rapidly acting effects on the circulatory system as direct sympathetic stimulation. That is, they excite the heart, constrict most of the blood vessels, and constrict the veins.
   - ✓ Norepinephrine has a generalized vasoconstrictor action, whereas epinephrine dilates the vessels in skeletal muscles and the liver.

2. The Renin-Angiotensin Vasoconstrictor system.
   The hormone **angiotensin II** is one of the most potent vasoconstrictors known.
   - ✓ Whenever the arterial pressure falls very low, large quantities of angiotensin II appear in the circulation. This results from a special mechanism involving the kidneys leading to the

release of the enzyme **renin** from the kidneys.

- ✓ Renin itself is an enzyme that splits the one of the plasma proteins, called **angiotensinogen or renin substrate**, releasing **angiotensin I.**
- ✓ Within a few seconds, angiotensin I is converted to angiotensin II. This conversion occurs almost entirely in the endothelial cells of the lungs, catalyzed by an enzyme called Angiotensin-converting enzyme (ACE).
- ✓ Renin persists in the blood for as long as one hour, and continues to cause formation of angiotensin I during this time. Angiotensin II persists in the blood for a minute or so, and is rapidly inactivated by a number of different blood and tissue enzymes collectively called angiotensinases.

Figure 3: The Renin angiotensin system

Actions of Angiotensin II:

Angiotensin II has several effects aiming to elevate the arterial pressure and to increase the ECF volume as follows:

1- It produces arteriolar vasoconstriction, increasing both systolic and diastolic blood pressure.
2- It acts on the adrenal cortex to increase the secretion of aldosterone hormone leading to salt and water retention.
3- It has a direct effect on the kidneys to cause increased salt

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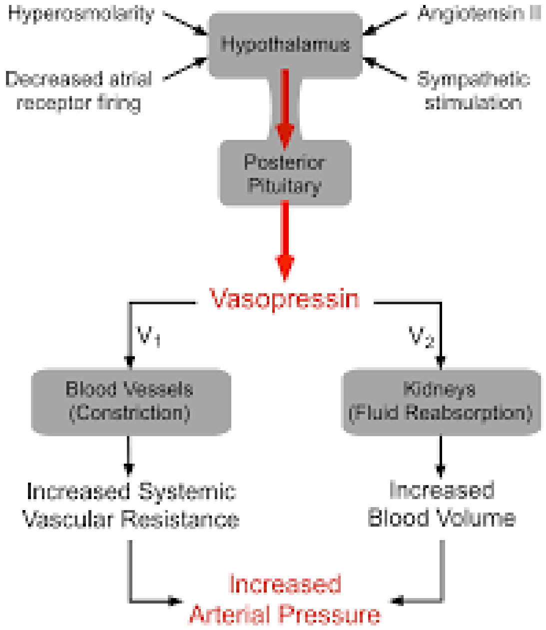
reabsorption.

4- It also acts on the brain to increase water intake (dipsogenic effect) and to increase vasopressin secretion.

5- Increase sympathetic activity



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3. <u>Antidiuretic hormone ADH (Vasopressin)</u>
   - ✓ It is the most potent vasoconstrictor substance.
   - ✓ Vasopressin is formed in the hypothalamus and stored in the posterior pituitary gland.
   - ✓ It is released into the circulation when:
     - The osmotic pressure of blood is increased (e.g. in dehydration or high salt intake).
     - It is also released when stimulation of atrial B receptors is reduced (e.g. hypovolemia).

✓Vasopressin has a marked constrictor effect on the systemic and renal arterioles; moreover, it reduces urine formation by the kidney that is why this hormone is called **antidiuretic hormone**.

b)Vasodilator hormones: include kinins and atrial natriuretic peptide

1. **<u>Kinins:</u>** Bradykinin and Lysylbradykinin are two vasodilator peptides found in the body.

Action of kinins:

The actions of kinins resemble those of histamine.

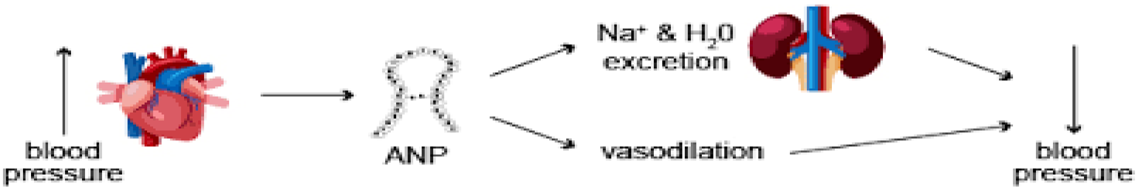
- ✓ They relax vascular smooth muscles via EDRF: lowering blood pressure.
- ✓ They increase capillary permeability and attract leucocytes.
- ✓ They are responsible for the increase in blood flow in certain tissues when they are actively secreting e.g. sweat glands, salivary glands and exocrine portion of pancreas.

2. <u>Atrial Natriuretic Peptide</u>

- ✓ It is released in the circulation when the ECF volume increases or during water immersion. This lead to increases the venous return and the atrial walls are then stretched.
- ✓ It is an important regulator of blood volume and blood pressure

Actions of ANP:

- ✓ Has potent diuretic and natriuretic effects on the kidneys
- ✓ It dilates the resistance and capacitance blood vessels.



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II. <u>NEURAL CONTROL OF THE BLOOD VESSELES</u>

A. Sympathetic noradrenergic Control:

- Arterioles are under resting sympathetic tone. Continuous resting discharge from the vasomotor area to the blood vessels is called "**vasomotor tone**" that is responsible for the normal blood pressure.
- Increasing the level of sympathetic tone constricts the arterioles and causes organ blood flow to fall below normal. Conversely, vasodilation and increased organ blood flow can be caused by a reduction in the sympathetic vasoconstrictor nerves activity.
- Most sympathetic fibers release noradrenaline that acts on α-receptors on the smooth muscle producing contraction.

B. Cholinergic Neuronal Control:

- Cholinergic sympathetic nerves release acetylcholine, which indirectly

dilates vascular smooth muscle.

- Cholinergic sympathetic innervate blood vessels of the skeletal muscle.
- Parasympathetic nerves do innervate erectile tissue producing vasodilatation.
- Vasodilator nerves have little effect on total peripheral resistance